VuCOMP
2500 Dallas Parkway, Suite 500
Plano, TX 75093

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VuCOMP

M-Vu® Algorithm Engine User Manual

Federal Law restricts this device to sale by or on the order of a licensed Physician.

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M-Vu® Algorithm Engine User Manual

Manufacturer
VuCOMP, Inc.
2500 Dallas Parkway, Suite 500
Plano, TX 75093

Tel: 888.266.7462
Fax: 877.577.5658
E-mail: info@vucomp.com
Web: www.vucomp.com

EU Authorized Representative
Emergo Europe
Molenstraat 15
2513 BH The Hague
The Netherlands

Tel: (31) (0) 70 345-8570
Fax: (31) (0) 70 346-7299

VuCOMP Authorized Dealer:

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1 Introduction

An M-Vu CAD System is composed of an M-Vu CAD Station, M-Vu Algorithm Engine, and any number of M-Vu Viewer Stations. This User Manual provides essential information about VuCOMP's M-Vu Algorithm Engine.

Do not use the M-Vu Algorithm Engine without proper training. Operator training and review of the user manuals for the M-Vu Viewer Station and M-Vu CAD Station are required prior to using the M-Vu CAD System.

2 Installation

The M-Vu Algorithm Engine software is installed on the M-Vu CAD Station by VuCOMP. The M-Vu CAD System must be installed on-site by a VuCOMP-authorized technician.

3 Warnings, Cautions, and Advisories

Do not use the M-Vu Algorithm Engine without proper training. Operator training and review of the user manuals for the M-Vu Viewer Station and M-Vu CAD Station are required prior to using the M-Vu CAD System.

Radiologists must review mammograms in the conventional manner prior to reviewing the M-Vu Algorithm Engine CAD results. Reviewing the M-Vu Algorithm Engine CAD results before reviewing the films could cause the radiologist to fail to examine the unmarked areas with adequate care.

Radiologists must not use the M-Vu Viewer Station images to interpret a mammogram. These images do not have the level of detail that exists in a film mammogram. Their only purpose is to provide a reference for the location of CAD marks.

The M-Vu Algorithm Engine will not mark all regions that contain cancer.

The M-Vu Algorithm Engine will mark regions that do not contain cancer.

The M-Vu Algorithm Engine CAD results assist only in the detection of suspicious regions of the mammogram. Therefore, the presence of a mark only indicates that a radiologist should review the marked region again to avoid a potential oversight, and the absence of a mark should not dissuade a radiologist from investigating suspicious findings.

The M-Vu Algorithm Engine may not mark the same lesion in both views.

Mass false positives can occur on benign masses, lymph nodes, blood vessels, crossing structures, skin folds, and areas of higher density caused by normal parenchymal structures.

Calcification false positives can occur on vascular calcifications, lucent calcifications, secretory calcifications, and small breast tissue structures. Calcification false positives can also occur on artifacts such as those caused by deodorant, powders, or other types of ointments on the skin.

The M-Vu Algorithm Engine is not designed to detect skin thickening or nipple retraction.

The M-Vu Algorithm Engine will not detect changes from prior mammograms.

The M-Vu Algorithm Engine is not intended to analyze views containing a breast that is too large to fit on the film.

The M-Vu Algorithm Engine is not intended for diagnostic purposes. Effectiveness has not been established for diagnostic views (e.g., magnification or compression views). These views should not be analyzed with the M-Vu Algorithm Engine.

The M-Vu Algorithm Engine is not intended to analyze implant views that include an implant. Effectiveness has not been established for implant views that include the implant.

The M-Vu Algorithm Engine may be used to analyze implant-displaced views.

The M-Vu Algorithm Engine may produce different results for the same film mammogram when it is repeatedly digitized and processed. Repeated digitization of the same mammogram results in slight variations in the digital image.

The M-Vu Algorithm Engine only supports the Craniocaudal (CC) and Mediolateral Oblique (MLO) views.

The M-Vu Algorithm Engine may not detect all errors in film orientation and labeling. All films must be digitized in the proper orientation and labeled with the appropriate view (LCC, RCC, LMLO, or RMLO).

The M-Vu Algorithm Engine does not support processing more than four views per case.

Films submitted to the M-Vu Algorithm Engine must meet MQSA standards. Only the standard mammographic film sizes are supported: 18x24 cm and 24x30 cm.

The M-Vu Algorithm Engine is not intended to analyze printed film from full-field digital mammography.

The M-Vu Algorithm Engine is not intended to analyze film copies.

All films must be clean, dry, and free from marks prior to scanning. The quality and cleanliness of films submitted to the M-Vu Algorithm Engine may impact the quality of the resulting analysis.

There are no known direct risks to safety or health of the user or the patient that are related to the use of the device. Indirect risks include:

1. The device may not mark actionable areas.
2. The device may mark regions that are not actionable.

4 M-Vu Algorithm Engine Overview

The M-Vu Algorithm Engine is a Computer-Aided Detection (CAD) software device intended to aid Radiologists in reading mammograms. It is a proprietary software application designed to process digitized film mammograms. The digital images are automatically analyzed to mark areas for review by a radiologist. Results are displayed on either a monitor or printed case report.

Do not use the M-Vu Algorithm Engine without proper training. Operator training and review of the user manuals for the M-Vu Viewer Station and M-Vu CAD Station are required prior to using the M-Vu CAD System.

Radiologists must review mammograms in the conventional manner prior to reviewing the M-Vu Algorithm Engine CAD results. Reviewing the M-Vu Algorithm Engine CAD results before reviewing the films could cause the radiologist to fail to examine the unmarked areas with adequate care.

4.1 Intended Use

The M-Vu Algorithm Engine is intended for use in screening mammography to identify areas consistent with breast cancer for Radiologist review after completing an initial read.

4.2 Contraindications

There are no contraindications for the use of this device.

5 Training Requirements

5.1 Overview

End users of the M-Vu CAD System must be trained prior to system use in a clinical environment. Training is provided by VuCOMP-authorized personnel and includes: intended use, performance specifications, network configuration, data workflow, functional operation, safety precautions, and service and support requirements.

5.2 Technologist Training Requirements

Technologists must be able to correctly operate the M-Vu CAD Station and Viewer Station. Technologists must demonstrate appropriate knowledge and skills in the following items:

- Identify the intended use of the CAD Station and Viewer Station;
- Identify CAD Station and Viewer Station warnings and cautions;
- Initialization and rebooting of the CAD Station and Viewer Station;
- HASP license key requirements;
- Modification of user settings related to printing and password control;
- Successfully log in to the CAD Station and Viewer Station;
- Identify the elements and functions of the CAD Screen;
- Display the CAD Station licensing information;
- Identify the elements and functions of the interfaces for CAD Station and Viewer Station;
- Demonstrate how to manually select images for CAD processing;
- Demonstrate how to filter completed cases by selecting a date or range of dates;
- Identify the purpose of the Loader Screen;
- Demonstrate how to load cases and delete cases;
- Demonstrate how to change the film display order;
- Demonstrate how to change the default multi-viewer panel settings;
- Demonstrate how to clear all cases stored in the viewer panels; and
- Identify the service and maintenance requirements for the CAD Station and Viewer Station.

5.3 Radiologist Training Requirements

Radiologists must have a full understanding of the M-Vu CAD System functions and capabilities including the following:

- Identify the intended use of the Algorithm Engine;
- Identify Algorithm Engine warnings and cautions;
- Identify the key performance characteristics of the Algorithm Engine;
- Successfully log in to the Viewer Station;
- Identify when it is appropriate to review CAD results on the Viewer Station;
- Identify when it is acceptable to interpret images on the Viewer Screen;
- Identify the elements and functions of the Viewer Screen;
- Demonstrate how to show/hide CAD marks;
- Identify the characteristics of a calcification CAD mark;
- Identify the characteristics of a mass CAD mark;
- Demonstrate how to show/hide patient IDs; and
- Demonstrate how to print CAD reports.

6 M-Vu Algorithm Engine

6.1 Description

The M-Vu Algorithm Engine searches a digitized screen-film mammogram for masses and microcalcification clusters that may be associated with breast cancer. It outlines regions of interest with solid lines (mass marks) to indicate possible masses and with dotted lines (calcification marks) to indicate possible microcalcification clusters.

The M-Vu Algorithm Engine will not mark all regions that contain cancer.

The M-Vu Algorithm Engine will mark regions that do not contain cancer.

The M-Vu Algorithm Engine CAD results assist only in the detection of suspicious regions of the mammogram. Therefore, the presence of a mark only indicates that a radiologist should review the marked region again to avoid a potential oversight, and the absence of a mark should not dissuade a radiologist from investigating suspicious findings.

The M-Vu Algorithm Engine may not mark the same lesion in both views.

Mass false positives can occur on benign masses, lymph nodes, blood vessels, crossing structures, skin folds, and areas of higher density caused by normal parenchymal structures.

Calcification false positives can occur on vascular calcifications, lucent calcifications, secretory calcifications, and small breast tissue structures. Calcification false positives can also occur on artifacts such as those caused by deodorant, powders, or other types of ointments on the skin.

The M-Vu Algorithm Engine is not designed to detect skin thickening or nipple retraction.

The M-Vu Algorithm Engine will not detect changes from prior mammograms.

6.1.1 Masses

The system searches for mass signs such as architectural distortions, spiculated lesions, ill-defined masses, well-defined masses, and asymmetric densities. The system can detect masses with a diameter between 5 mm and 5 cm. Each detected area is enclosed by a mass mark consisting of a solid red line. A single mass mark may contain more than one type of mass sign. Figure 6-1 shows examples of mass true positives.

False positives can occur on benign masses, lymph nodes, blood vessels, crossing structures, skin folds, and areas of higher density caused by normal parenchymal structures. Figure 6-2 shows examples of mass false positives.

6.1.2 Microcalcification Clusters

The system searches for signs of microcalcification clusters composed of three or more individual microcalcifications. The system considers the relative spacing of calcifications in a cluster as well as the appearances of the individual calcifications. The system can detect an individual microcalcification between 0.2 mm and 0.6 mm in diameter. Each detected area is enclosed by a calcification mark consisting of a dotted red line. Figure 6-3 shows examples of calcification true positives.

False positives can occur on vascular calcifications, lucent calcifications, secretory calcifications, and small breast tissue structures. False positives can also occur on artifacts such as those caused by deodorant, powders, or other types of ointments applied to the skin. Figure 6-4 shows examples of calcification false positives.

Figure 6-1: M-Vu Mass True Positives

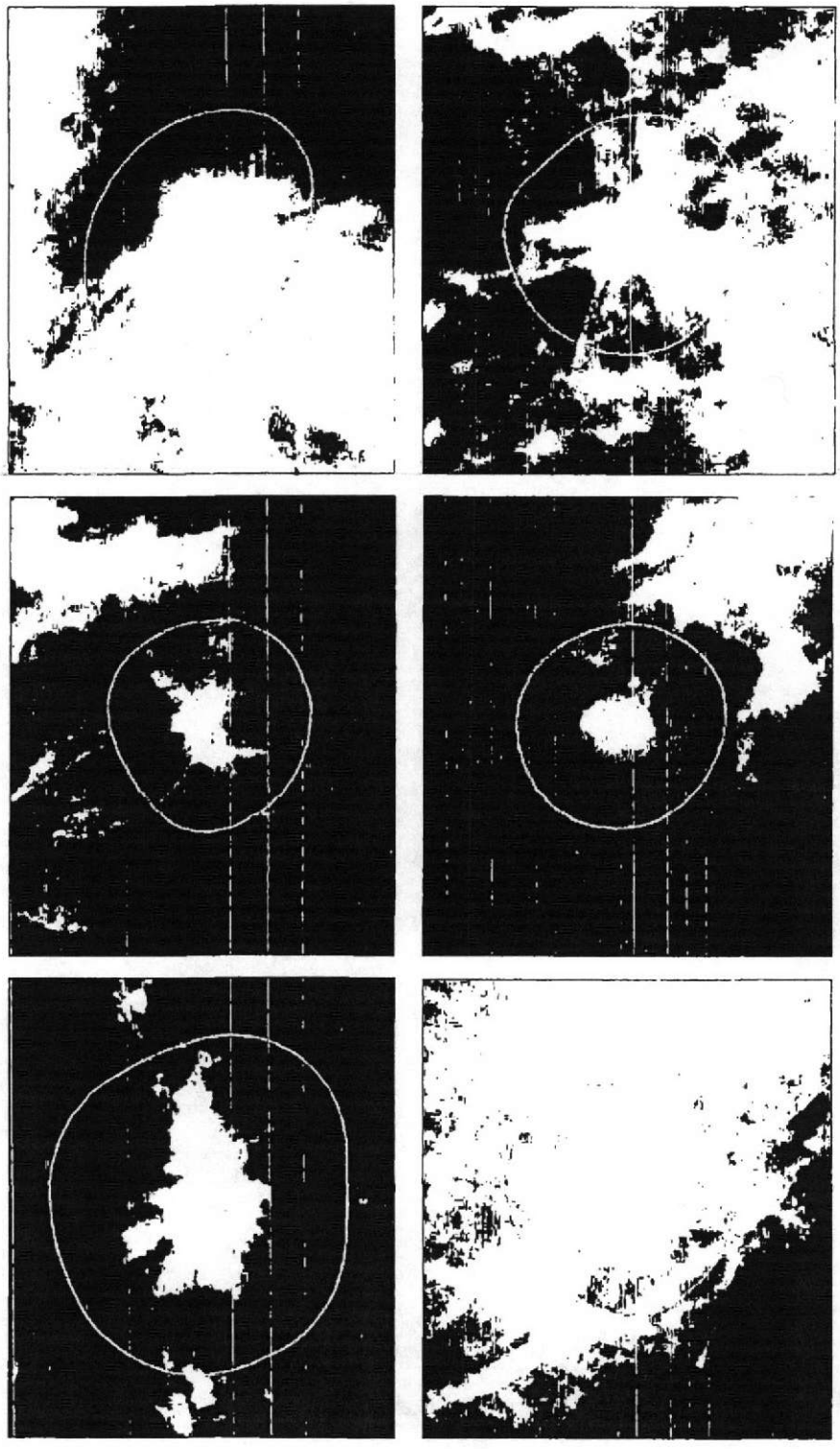


Figure 6-2: M-Vu Mass False Positives

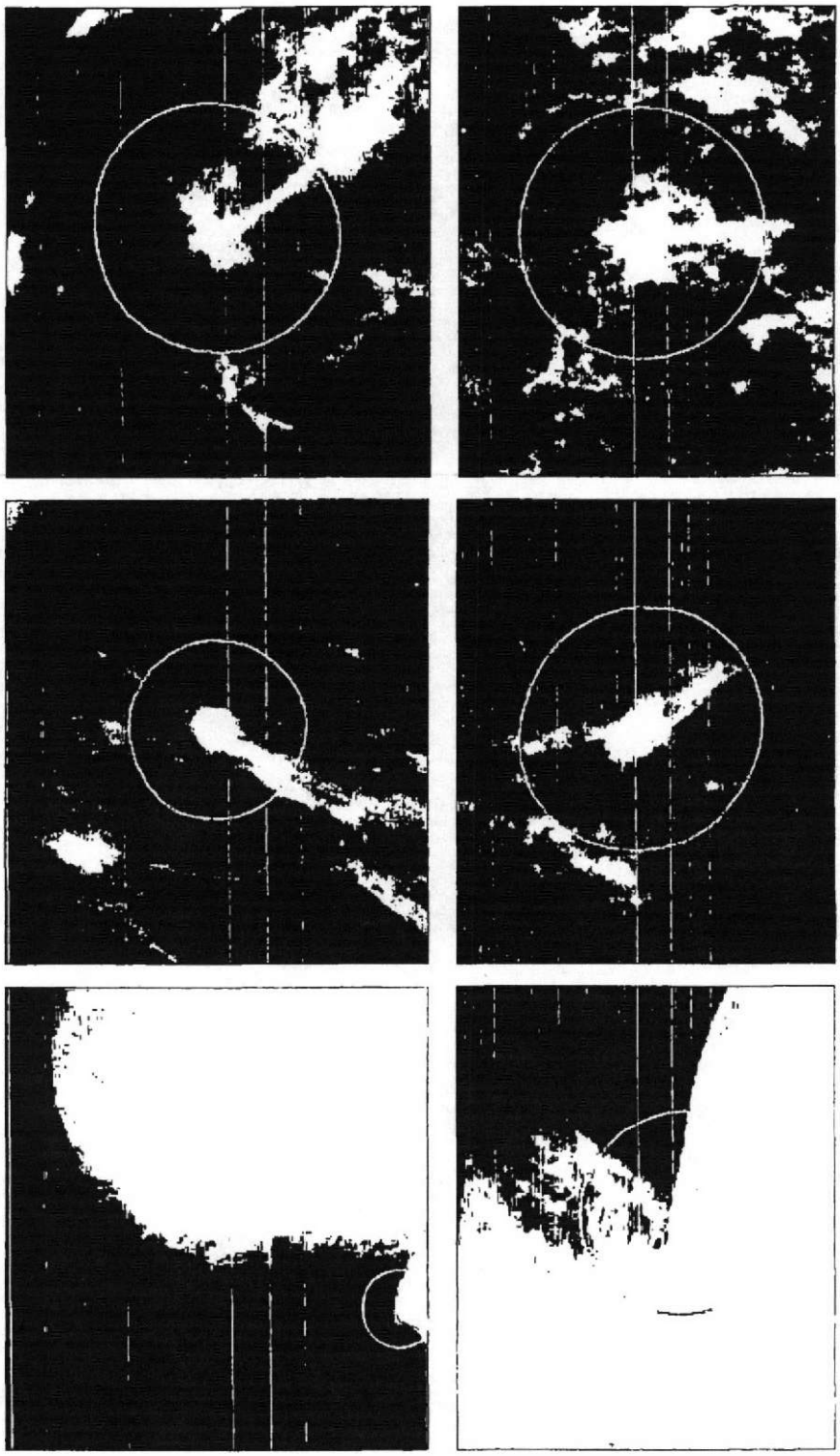


Figure 6-3: M-Vu Calcification True Positives

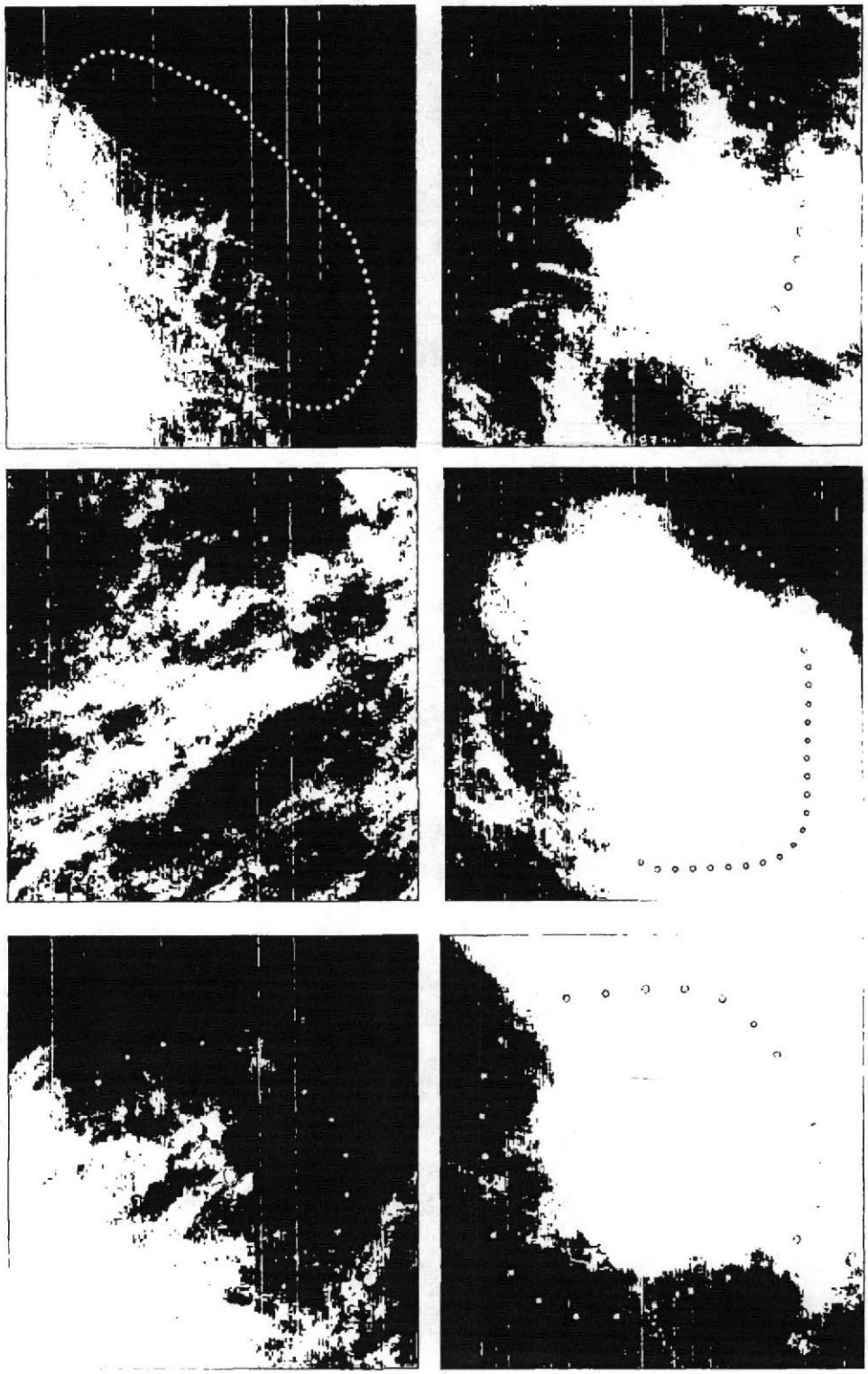
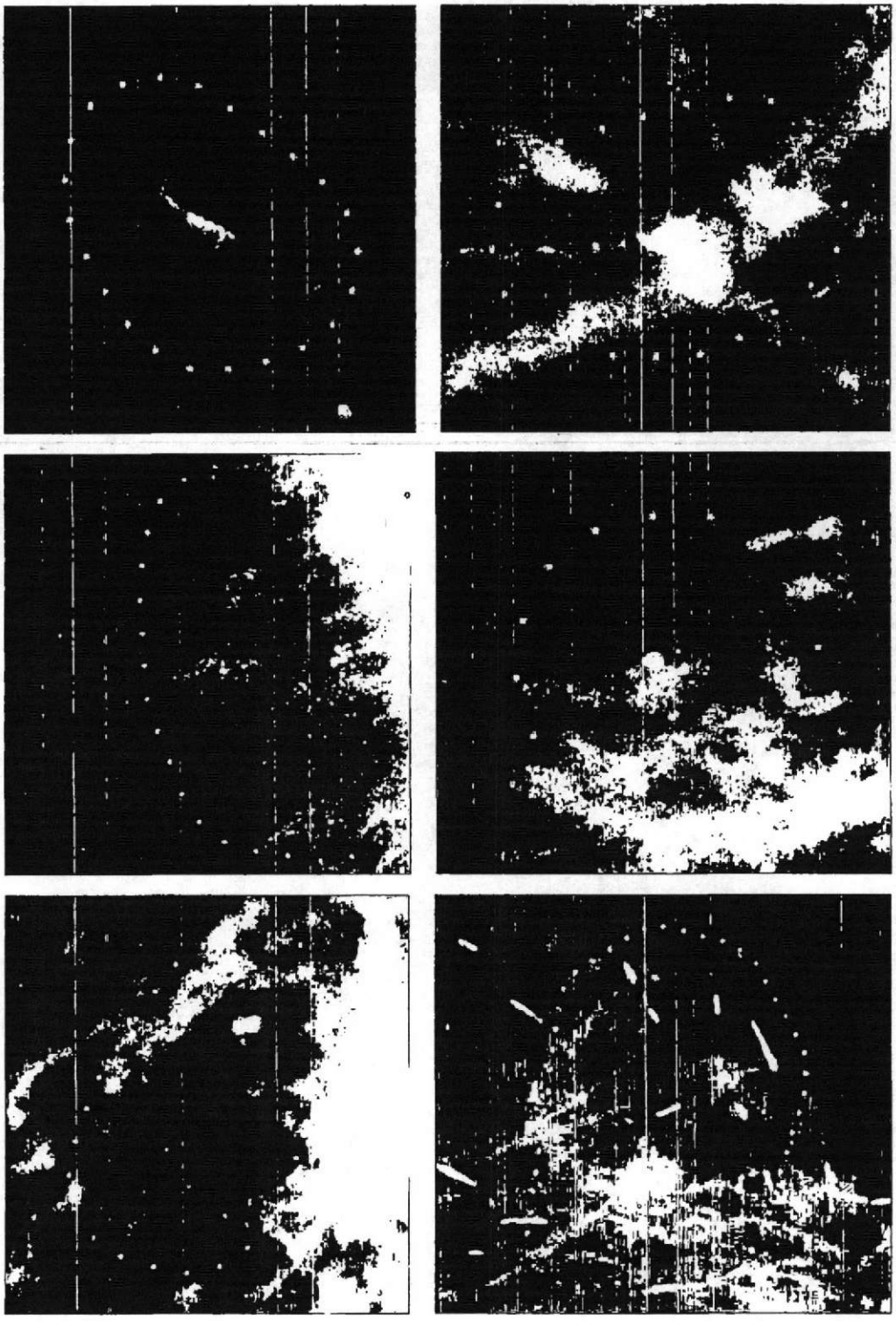


Figure 6-4: M-Vu Calcification False Positives



6.2 M-Vu CAD System Operation

The M-Vu CAD System is composed of three main parts: the CAD Station, Algorithm Engine, and Viewer Station. The CAD Station receives digitized mammograms, runs the Algorithm Engine, prints case reports, and sends results to a Viewer Station. The Algorithm Engine analyzes the digitized mammograms and produces CAD marks that indicate areas of a mammogram for radiologist review. The Viewer Station orders the results and displays them on a monitor for review.

Do not use the M-Vu Algorithm Engine without proper training. Operator training and review of the user manuals for the M-Vu Viewer Station and M-Vu CAD Station are required prior to using the M-Vu CAD System.

6.2.1 Film Digitizer Operation

Mammogram films must be digitized with a 2908 Mammo Pro Laser Film Digitizer manufactured by Array Corporation. Digitized films may be sent to a CAD Station over a local area network either directly from a digitizer or through a PACS system.

Note: Please refer to the user manuals of the Mammo Pro and your PACS system for details of their operation.

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The M-Vu Algorithm Engine may produce different results for the same film mammogram when it is repeatedly digitized and processed. Repeated digitization of the same mammogram results in slight variations in the digital image.

The M-Vu Algorithm Engine does not support processing more than four views per case.

The M-Vu Algorithm Engine only supports the Craniocaudal (CC) and Mediolateral Oblique (MLO) views.

The M-Vu Algorithm Engine may not detect all errors in film orientation and labeling. All films must be digitized in the proper orientation and labeled with the appropriate view (LCC, RCC, LMLO, or RMLO).

Films submitted to the M-Vu Algorithm Engine must meet MQSA standards. Only the standard mammographic film sizes are supported: 18x24 cm and 24x30 cm.

The M-Vu Algorithm Engine is not intended to analyze printed film from full-field digital mammography.

The M-Vu Algorithm Engine is not intended to analyze film copies.

All films must be clean, dry, and free from marks prior to scanning. The quality and cleanliness of films submitted to the M-Vu Algorithm Engine may impact the quality of the resulting analysis.

6.2.2 CAD Station Operation

The CAD Station is a DICOM Service Class User (SCU), which allows passive reception of images over a local area network. The CAD Station will accept standard mammography screening views (RCC, LCC, RMLO, and LMLO). If the CAD Station receives more than one image of a view for a case, it will only use the last image received. After the CAD Station has received the images for a case, it will immediately place them into a queue for analysis by the Algorithm Engine. The CAD Station will automatically print a case report after the Algorithm Engine has completed analysis for a case.

Note: Please refer to the user manual of the M-Vu CAD Station for details of its operation.

6.2.3 Viewer Station Operation

The Viewer Station provides a user interface (the Loader Screen) to allow a technologist to select and order the CAD results and another user interface (the Viewer Screen) to allow a radiologist to view the CAD results on a monitor.

The Loader Screen can be accessed by clicking the LOAD PANELS button in the bottom-left corner of the screen. The Loader Screen is organized into a sequence of numbered panels. This sequence determines the order that CAD results will be displayed to a radiologist on the Viewer Screen. The panels can be used to correspond to panel numbers on a film multi-viewer or to an ordering of cases that a radiologist will view on a lightbox. Three panels are displayed on the Loader Screen at one time – the previous panel, the current panel, and the next panel. The current panel is highlighted in white, while the other two are gray. The mouse wheel allows selection of any panel as the current panel.

Using the barcode reader to scan the unique barcode at the top of a printed case report will cause the Viewer Station to pull the corresponding CAD results and mammogram images for that case from the CAD Station and load them into the current panel. After loading a panel, the Loader Screen will automatically advance to the next panel. A technologist can repeat this process to load all of the CAD results for a viewing session in a particular order.

After a technologist has ordered the CAD results in the Loader Screen, a radiologist can easily review the ordered results using the Viewer Screen.

The Viewer Screen can be accessed by clicking the VIEW CASES button in the bottom-left corner of the screen. The Viewer Screen will show a low-resolution version of the digitized mammogram for a case. The top-left corner of the screen shows the current panel number. The top-right corner of the screen shows the date the case was processed and the case number. The mouse wheel allows display of any panel. Once the radiologist has read the films for a case, she can click the left mouse button to display the case's CAD marks on the Viewer Screen. Another left-click will advance to the next panel showing images of the mammogram with no CAD marks. This process is repeated to view the CAD results in the order previously defined by the technologist.

Note: Please refer to the user manual of the M-Vu Viewer Station for details of its operation.

Radiologists must review mammograms in the conventional manner prior to reviewing the M-Vu Algorithm Engine CAD results. Reviewing the M-Vu Algorithm Engine CAD results before reviewing the films could cause the radiologist to fail to examine the unmarked areas with adequate care.

Radiologists must not use the M-Vu Viewer Station images to interpret a mammogram. These images do not have the level of detail that exists in a film mammogram. Their only purpose is to provide a reference for the location of CAD marks.

7 Clinical Studies

7.1 Clinical Studies Overview

The primary objective of the clinical studies was to determine whether radiologists are more effective at reading screen-film mammograms when using the M-Vu Algorithm Engine versus when not using Computer-Aided Detection (CAD).

The University of North Carolina (UNC) served as the Clinical Research Organization for this study under the direction of the Primary Investigator, Etta D. Pisano, MD. The following retrospective studies were performed:

- A pivotal reader study to compare the effectiveness of radiologists reading screen-film mammograms when using the M-Vu Algorithm Engine versus when not using CAD.
- A CAD standalone study to measure behavior of the M-Vu Algorithm Engine separately from the radiologists.

7.2 Reader Study

7.2.1 Readers and Cases

The Pivotal Study used 21 radiologists reading 280 cases. The radiologists were from a variety of academic, specialty, and community clinics located across the United States.

The cases were a randomly selected set of 140 positive cases and 140 negative cases drawn from 11 United States sites representing academic, specialty, and community clinics. Each site received approval to provide cases for this study by their respective Institutional Review Boards. The cases were selected such that no more than 10% of the positive cases and no more than 10% of the negative cases came from any one site.

A positive case was defined as an exam having a biopsy-proven breast cancer found within 15 months following the exam date. A negative case was defined as an exam for which breast cancer had not been found within 15 months prior or 15 months after the exam date, and for which at least one associated subsequent negative exam had been taken at least 11 months after the exam date. The inclusion and exclusion criteria were as follows:

Inclusion Criteria:

- Cases are screen-film mammograms from exams performed during the years 1998 through 2006.
- Patients who are female and at least 18 years of age, having had a mammography exam and relevant history for determining positive or negative status.
- Cases that include four views: LCC, RCC, LMLO, and RMLO (two for unilateral studies).

Exclusion Criteria:

- Cases that are diagnostic (e.g., to explore palpable lesions or other symptoms) instead of screening.
- Cases that include any film copies.
- Cases with implants but no implant-displaced views.
- Cases not acquired from an MQSA certified facility.
- Cases without sufficient patient information to facilitate truthing, which includes basic demographic information (age, race, ethnicity) and appropriate radiology reports, biopsy reports, and pathology reports as necessary within two years after mammogram date.
- Cases of patients who were either pregnant or nursing at the time of imaging.
- Cases with film containing indelible marks, or markers in film intended to indicate prior biopsy sites (scars).
- Cases otherwise not meeting the inclusion criteria.

Each site submitted original screen-film mammograms, acetate overlays indicating the location of each known cancer, de-identified clinical reports (including radiology, surgical, and pathology reports), and study-specific case report forms.

7.2.2 Reader Study Execution

The clinical studies were conducted at the University of North Carolina (UNC) located in Chapel Hill, North Carolina. Care was taken to mimic the clinical environment of a radiology lab during the study. Environmental conditions similar to a typical clinical environment were established, including temperature, ambient light, light sources (less than 50 lux), level of comfort, level of furnishings, and ambient noise.

Cases were presented to the readers in random order. For each case, each reader performed the following actions in order:

1. Evaluate the case without seeing marks from the M-Vu Algorithm Engine
2. Record a "without CAD" assessment for the case
3. View the marks created by the M-Vu Algorithm Engine for the case
4. Record a "with CAD" assessment for the case

The "with CAD" and "without CAD" assessments included the following information:

- Whether the reader would recall the patient, and why (suspicious finding or technical problem)
- Screening BI-RADS (0, 1, 2, 3, 4a, 4b, 4c, 5)
- Forced BI-RADS (1, 2; 3, 4a, 4b, 4c, 5) if screening BI-RADS was "0"
- Lesion findings

The lesion findings included the following information for each individual lesion finding:

- Laterality (left or right)
- Type (Mass, Architectural Distortion, Asymmetry, or Calcification)
- BI-RADS (1, 2, 3, 4a, 4b, 4c, 5)
- Probability of Malignancy (0-100%)

7.2.3 *Pivotal Study Statistical Methods*

We estimated a smooth receiver operating characteristic (ROC) curve[1,2] for each of the 21 study readers in each test condition (without CAD and with CAD) using the probability of malignancy (POM) ratings he or she provided. Each ROC curve was estimated using proper ROC models in DBM MRMC software[3]. For each reader, we computed differences between the readings with CAD and without CAD in terms of area under the ROC curve, and we quantified uncertainty using 95% confidence intervals while taking into account correlations that arose because each reader interpreted the same cases in both conditions. We used the method of Dorfman, Berbaum, and Metz[4] with proper binormal models and random effects for readers in DBM MRMC software[3] to perform multi-reader, multi-case (MRMC) analysis and compare area under the ROC curve between conditions. We also used MRMC methods with fixed effect for reading condition and random effects for readers to analyze FROC curves[5], sensitivities (per-case and per-lesion), specificities (per-case), and false-positive marks per image[6]. Subgroup analyses looked particularly at results for masses and for calcifications.

In all analysis using BI-RADS category, a "forced BI-RADS" value was used. This is a nonzero value (1, 2, 3, 4a, 4b, 4c, or 5) provided by the reader even if the reader would have normally used a value of zero in a screening context.

7.2.4 *Pivotal Study Primary Results*

The primary aim of the Pivotal Study was to determine if radiologists reading screen-film mammograms were more effective at finding cancer when using the M-Vu Algorithm Engine versus when not using CAD. This aim was further divided into 1) effectiveness in finding malignant lesions, and 2) effectiveness in finding malignant cases.

The effectiveness of the radiologists in finding malignant lesions was analyzed with the JAFROC figure of merit[8] (FOM), which provides an estimate of the probability that a reader rates malignant lesions as more suspicious than non-malignant findings. The measured figure of merit for radiologists using CAD was significantly larger ($p = 0.001$) than the figure of merit for the same radiologists interpreting the same cases without CAD (Table 7-1).

The effectiveness of the radiologists in finding malignant cases was analyzed with the area under the per-case ROC curve (AUC), which provides an estimate of the probability that a reader rates malignant cases as more suspicious than non-malignant cases. The average area under the per-case ROC curve for radiologists using CAD was significantly larger ($p = 0.013$) than the average area under the ROC curve for the same radiologists interpreting the same cases without CAD (Table 7-1). Figure 7-1 shows graphs of the ROC curve for the without-CAD and with-CAD conditions.

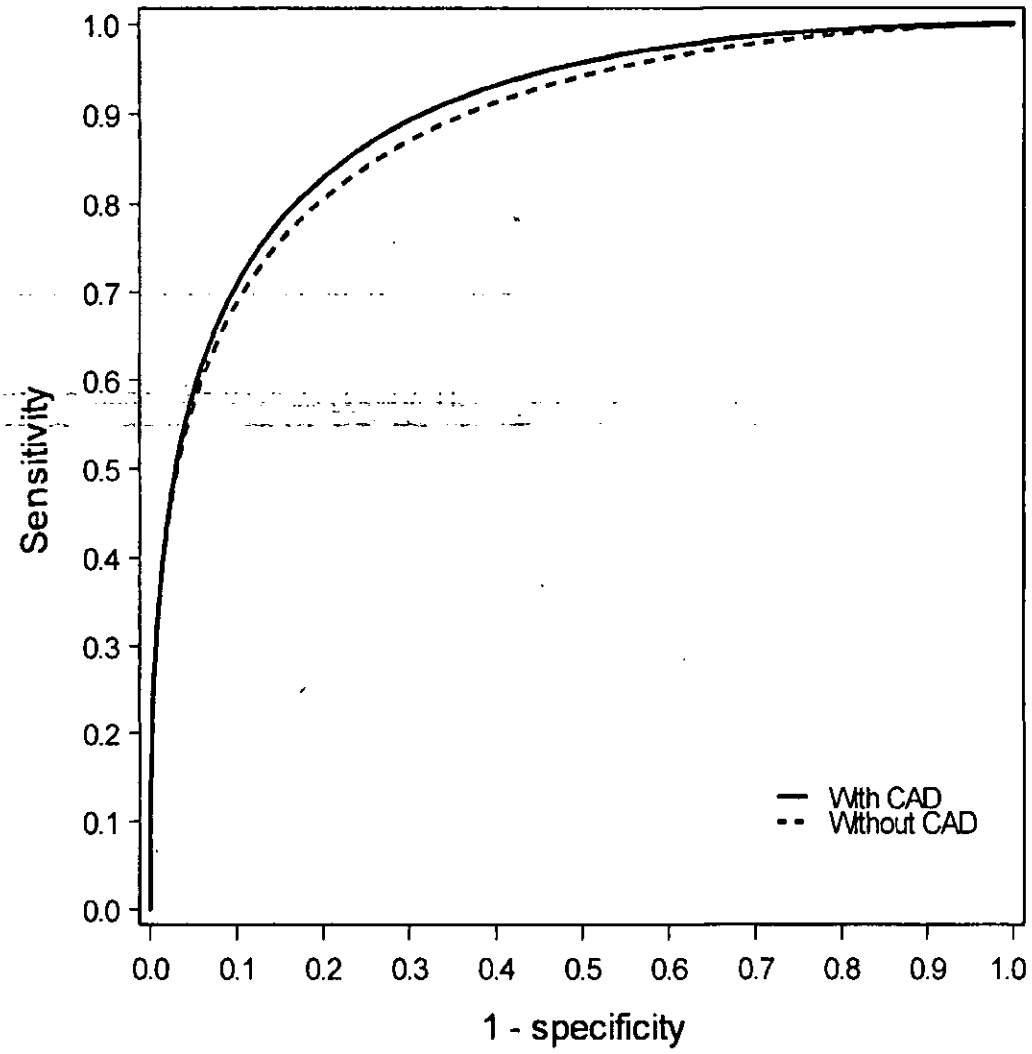
Table 7-1: Primary Results of Pivotal Study – JAFROC Figure of Merit (FOM) and Area under the Per-Case ROC Curve (AUC)

Analysis	Without CAD	With CAD	Difference (CI)	P-value
FOM	0.812	0.839	0.027 (0.012, 0.043)	0.001
AUC	0.885	0.902	0.016 (0.004, 0.029)	0.013

Difference = with CAD - without CAD.
CI = 95% Confidence Interval.

All primary aims of the study were met. **As a result, this study concludes that use of the M-Vu Algorithm Engine led to a significant increase in effectiveness for the group of 21 radiologists reading screen-film mammograms.**

Figure 7-1: Radiologist ROC Curves Based on Probability of Malignancy



7.2.5 *Pivotal Study Secondary Results*

Although the Pivotal Study was designed to only show statistical significance for the primary aims, additional secondary analysis was performed for informational purposes. This analysis included radiologist sensitivity, specificity, and area under the per-case ROC curve for two subgroups (masses and calcification clusters).

The average radiologist sensitivity (based on recall) increased significantly ($p < 0.002$) from 0.865 without CAD to 0.901 with CAD (Table 7-2). This represents an increase of 4.2% more cancers detected and 26.7% of missed cancers detected. Radiologist sensitivity also increased significantly for calcification cases ($p = 0.001$) and mass cases ($p = 0.016$). The overall sensitivity increase was accompanied by a smaller, but still statistically significant ($p < 0.001$) decrease in specificity (based on recall) from 0.649 to 0.623 (Table 7-5).

The average radiologist sensitivity (based on BI-RADS category 3 or higher) increased significantly ($p = 0.004$) from 0.851 without CAD to 0.885 with CAD (Table 7-3). Radiologist sensitivity also increased significantly for calcification cases ($p = 0.003$) and mass cases ($p = 0.036$). The overall sensitivity increase was accompanied by a smaller, but still statistically significant ($p = 0.001$) decrease in specificity (based on BI-RADS) from 0.684 to 0.658 (Table 7-5).

Table 7-2: Radiologist Per-Case Sensitivity Based on Recall

Group	Without CAD	With CAD	Difference (CI)	P-value
Overall	0.865	0.901	0.036 (0.014, 0.058)	0.002
Calcification	0.830	0.882	0.052 (0.021, 0.083)	0.001
Mass	0.897	0.918	0.021 (0.004, 0.038)	0.016

Difference = with CAD - without CAD.
CI = 95% Confidence Interval

Table 7-3: Radiologist Per-Case Sensitivity Based on BI-RADS Category

Group	Without CAD	With CAD	Difference (CI)	P-value
Overall	0.851	0.885	0.033 (0.011, 0.055)	0.004
Calcification	0.817	0.866	0.049 (0.017, 0.080)	0.003
Mass	0.885	0.904	0.018 (0.001, 0.035)	0.036

Difference = with CAD - without CAD.
CI = 95% Confidence Interval.

The average radiologist per-lesion sensitivity (based on BI-RADS category 3 or higher) increased significantly for the Overall ($p < 0.001$), Calcification ($p < 0.001$), and Mass ($p = 0.004$) groups (Table 7-4).

Table 7-4: Radiologist Per-Lesion Sensitivity Based on BI-RADS Category

Group	Without CAD	With CAD	Difference (CI)	P-value
Overall	0.792	0.834	0.043 (0.023, 0.063)	<0.001
Calcification	0.731	0.797	0.067 (0.034, 0.100)	<0.001
Mass	0.851	0.871	0.021 (0.007, 0.034)	0.004

Difference = with CAD - without CAD.
CI = 95% Confidence Interval.

Table 7-5: Radiologist Per-Case Specificity

Basis	Without CAD	With CAD	Difference (CI)	P-value
Recall	0.649	0.623	-0.026 (-0.039, -0.013)	<0.001
BI-RADS	0.684	0.658	-0.024 (-0.037, -0.011)	0.001

Difference = with CAD - without CAD.
CI = 95% Confidence Interval.

Analysis of the average area under the radiologist per-case ROC curve was divided into calcification and mass subgroups. The calcification ROC analysis used the 69 malignant calcification cases along with all 140 negative cases. The mass ROC analysis used the 86 malignant mass cases along with all 140 negative cases. All reader findings were used regardless of finding type. Consequently, to show improvement in the calcification ROC curve, the radiologist improvement in finding malignant calcifications must individually outweigh any specificity degradation due to both calcification false positives and mass false positives. Similarly, improvement in finding malignant masses must individually outweigh any specificity degradation due to both calcification false positives and mass false positives. This results in a very conservative estimate of improvement in radiologist performance for each subgroup. Table 7-6 shows that the area under the curve increased for both calcifications and masses despite the fact that false positives of all types were included. The increase was statistically significant for calcifications ($p = 0.007$), but not for masses ($p = 0.27$). Figures 7-2 and 7-3 show graphs of the ROC curves for the subgroups.

Table 7-6: Subgroup Analysis of Area under the Per-Case ROC Curve Based on Probability of Malignancy where specificity is calculated using false positives of all types (both calcification and mass)

Group	Without CAD	With CAD	Difference (CI)	P-value
Calcification	0.867	0.891	0.024 (0.007, 0.042)	0.007
Mass	0.910	0.914	0.004 (-0.004, 0.012)	0.27

Difference = with CAD - without CAD.
CI = 95% Confidence Interval.

Figure 7-2: Radiologist Calcification ROC Curves Based on Probability of Malignancy where specificity is calculated using false positives of all types (both calcification and mass)

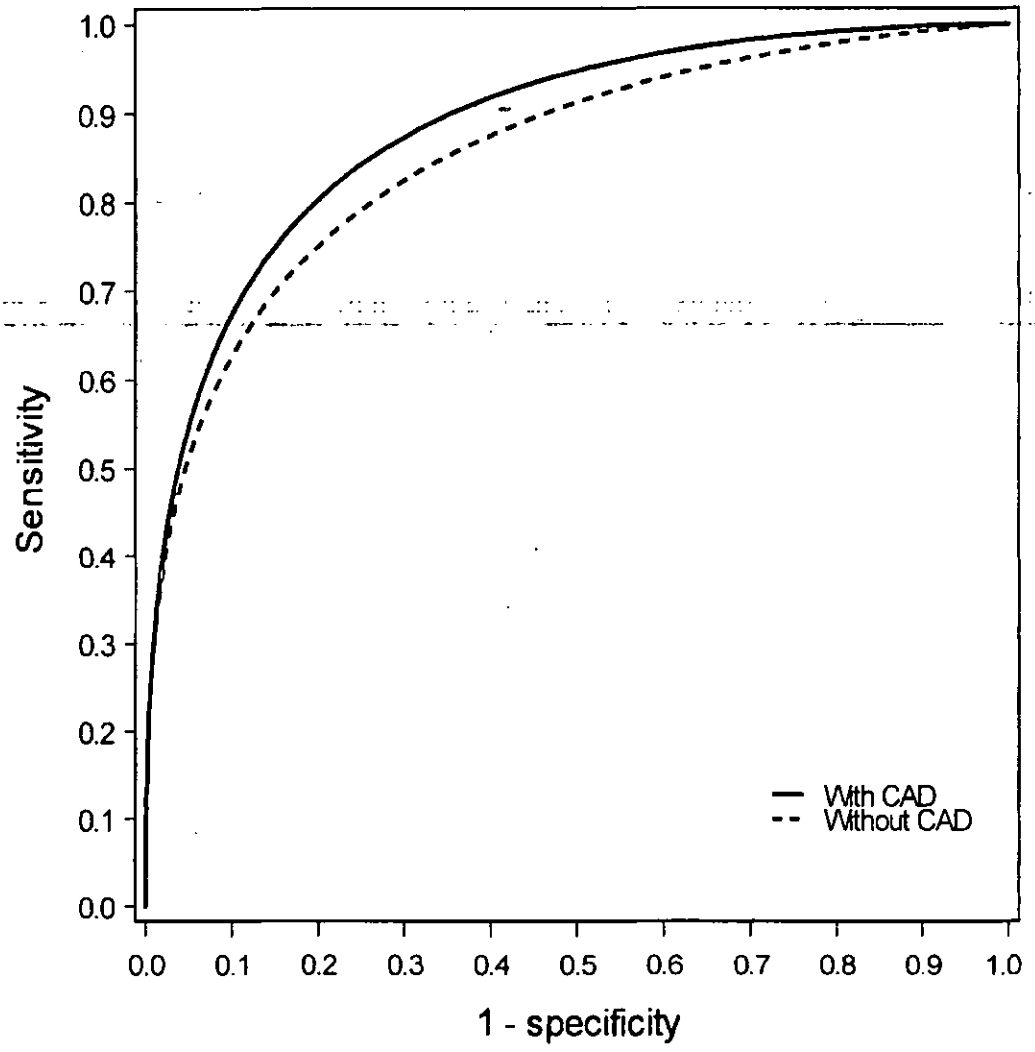
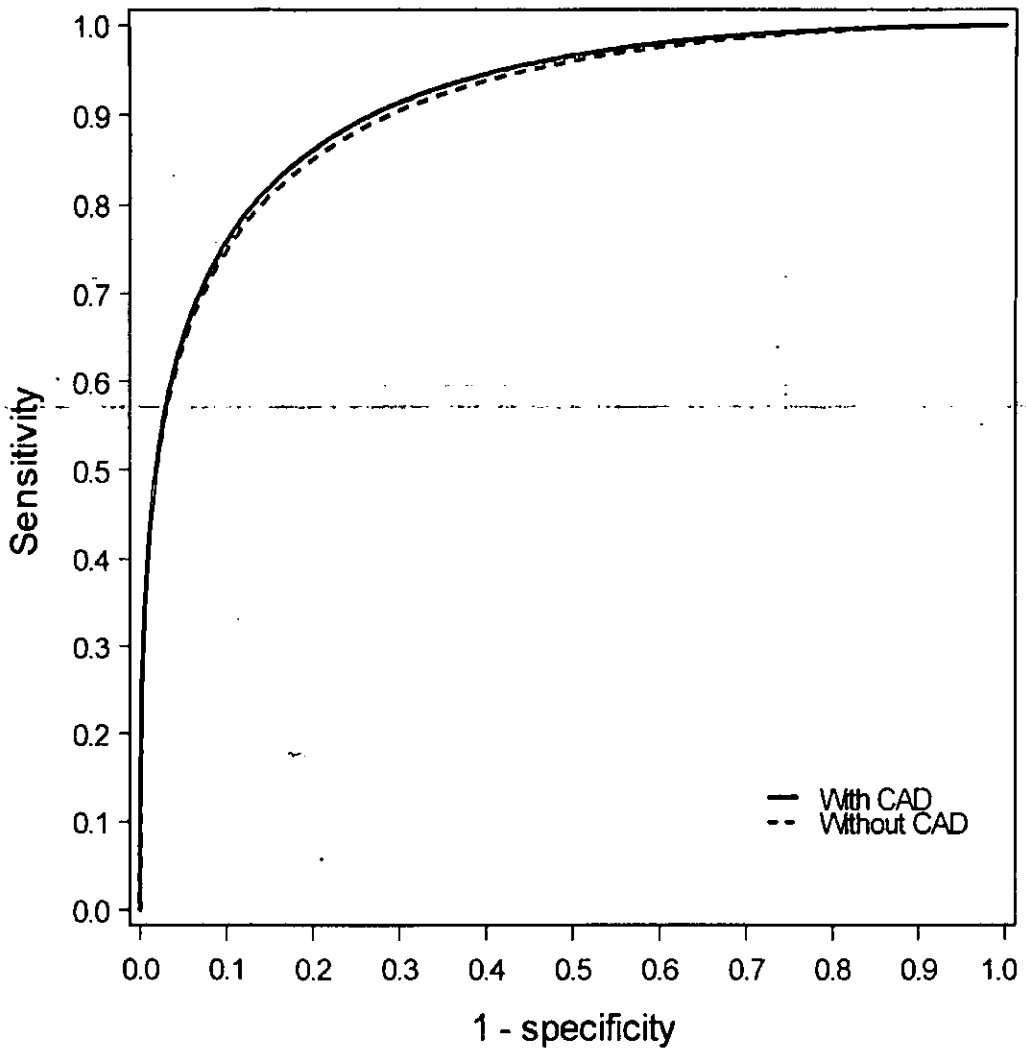


Figure 7-3: Radiologist Mass ROC Curves Based on Probability of Malignancy where specificity is calculated using false positives of all types (both calcification and mass)



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7.3 CAD Standalone Study

CAD sensitivity was measured as the proportion of cancer cases that were true positives. A case true positive occurred if a case had at least one malignant region found by CAD. A malignant region was considered found if a CAD mark centroid was inside the region or if the region centroid was inside a CAD mark. CAD specificity was measured as the proportion of negative cases that were true negatives. A case true negative occurred if a negative case had no CAD marks on it. Table 7-7 shows the CAD sensitivity on the 140 cancer cases used in the Pivotal Study. Table 7-8 shows the CAD sensitivity by lesion size. Table 7-9 shows the average CAD false positives per image (FPPI) for the 140 negative cases used in the Pivotal Study.

Table 7-7: CAD Sensitivity

	Cases	Sensitivity	Confidence Interval
Overall	140	79.3%	(72.6%, 86.0%)
Calcification	69	79.7%	(70.2%, 89.2%)
Mass	86	81.4%	(73.2%, 89.6%)

Table 7-8: CAD Sensitivity by Lesion Size with Confidence Intervals in Parenthesis

Lesion Size (mm)	Calcification Sensitivity	Mass Sensitivity	Overall Sensitivity
<= 8	7/13=53.8% (26.7%, 80.9%)	15/20=75.0% (56.0%, 94.0%)	21/31=67.7% (51.3%, 84.2%)
> 8 and <= 12.5	5/6=83.3% (53.5%, 100%)	16/21=76.2% (58.0%, 94.4%)	19/25=76.0% (59.3%, 92.7%)
> 12.5 and <= 17	12/12=100% (100%, 100%)	19/21=90.5% (77.9%, 100%)	26/28=92.9% (83.3%, 100%)
> 17	14/16=87.5% (71.3%, 100%)	13/15=86.7% (69.5%, 100%)	23/27=85.2% (71.8%, 98.6%)
No Measurement	17/22=77.3% (59.8%, 94.8%)	7/9=77.8% (50.6%, 100%)	22/29=75.9% (60.3%, 91.4%)

Table 7-9: CAD FPPI

	Images	FPPI	Confidence Interval
Overall	560	0.418	(0.346, 0.490)
Calcification	560	0.088	(0.042, 0.133)
Mass	560	0.330	(0.275, 0.385)

Due to the randomness of the film digitization process, no two images created by a film digitizer are ever exactly the same. This causes some variation in the CAD results.

The repeatability of cancer detection was measured by randomly selecting 27 cancer cases, scanning them multiple times on multiple digitizers, running each case's scans through CAD, and then analyzing how often outcomes (either true positive case or false negative case) were repeated. Three different MammoPro film digitizers (Array Corporation USA, Hampton, NH) were used. Each case was scanned 10 times (3 times on one digitizer, 3 times on another, and 4 times on the third). Repeatability was measured as the proportion of the number of outcomes that were in the majority. Mathematically, this is expressed by $max(TP, FN)/(TP + FN)$, where TP is the number of true positive case outcomes and FN is the number of false negative case outcomes. Table 7-10 shows the CAD repeatability over the 27 cancer cases and 3 film digitizers.

Table 7-10: CAD Repeatability with Confidence Intervals in Parenthesis

Overall	Scanner A	Scanner B	Scanner C
0.922 (0.866, 0.979)	0.963 (0.923, 1.000)	0.963 (0.923, 1.000)	0.944 (0.897, 0.992)

7.4 Conclusions Drawn from Studies

Use of the M-Vu Algorithm Engine led to an increase in effectiveness of the group of 21 radiologists reading screen-film mammograms. This was demonstrated as an improved ability to discriminate between malignant and non-malignant cases. Additionally, radiologist sensitivity increased, while specificity decreased by a smaller amount. All of these effects were statistically significant.

8 References

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